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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/186,475	11/04/1998	ANNIE FONG	238/046	1830

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	26

DATE MAILED: 10/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/186,475	FONG ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-3,6,8-11,16-21,23,24 and 27-32* is/are pending in the application.

4a) Of the above claim(s) *19-21 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3,9-11,23,24 and 28-32* is/are rejected.

7)☐ Claim(s) *6 and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. The request filed on April 21, 2003 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/186,475 is acceptable and a CPA has been established. An action on the CPA follows.

2. Please note that the examiner assigned to this application is changed..

3. Claims 4, 5 and 7 have been canceled. Claim 1 has been amended. Claims 1-3, 6, 8-11, 16-21, 23, 24 and 27-32 are pending. Claims 19-21 and 27, drawn to non-elected species, are withdrawn from consideration. Claims 1-3, 6, 8-11, 16-18, 23, 24 and 28-32 are under consideration.

4. It is noted that the instant application was subject to an election of species in Paper No. 10, mailed May 24, 2001, and the response to that species of election was summarized in Paper No. 12:

> Applicant has elected the following species:
> (A) Disease etiology-specifically cancer
> (B) Angiogenesis receptors-flk-1
> (C) Antagonist-compound A (as set forth in claim 8)
> (D) Sample type- whole blood or fraction thereof
> (E) Angiogenesis markers- protein phosphorylation by measuring a protein
> (F) Assay type-antibody assay
> (G) Specific assay-detection with antibodies.

5. After review and reconsideration, the search for species (A) will be expanded to cell proliferation when examined with the species of (C) (compound A).

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action..

7. Claims 6 and 8 are objected to for depending on a canceled claim. Accordingly, claims 6 and 8 are withdrawn from consideration. Claim 23 is objected to for depending in part on claim 15 which is canceled. Claim 23 will be examined to the extent that it reads on examined claims 16-18.

8. Claim17 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. the recitation of "determining the presence or amount of said marker" in claim 17 does not further limit the scope of claim 1, which contains the specific embodiment of "monitoring a marker", because monitoring a marker includes quantitative as well as qualitative measurements.

9. Claims 1-3, 9-11, 16-18, 23, 24 and 28-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claim 1 recites limitation (c) of constructing a standard curve and limitation (d) of determining the efficacious dose based on the standard curve without specific method steps defining said construction and determination. It is well known in the art that a mathematical "curve" is a function of at least two parameters, however, the claims do not limit what either of said parameters can consist of. With regard to section d, the claims do not set forth an active, positive method step to carry out the claimed determination. Section 2173.05(q) of the MPEP states

> Attempts to claim a process without setting forth any steps involved in the process generally raises an issue of indefiniteness under 35 U.S.C. 112, second paragraph. Therefore without positive active methods steps for sections c and d of claim 1, the claims are indefinite.

(B) Claim 24 recites the limitation of comparing a marker to a "standard". The metes and bounds of the claim cannot be determined because there is not specific definition of what constitutes said "standard".

(C) Claims 29 and 30 recite the limitation of "additional amounts" However, it is unclear what the term "additional" is in reference to. thus without a starting point for an amount, the metes and bounds of what constitutes an "additional amount" is unclear.

(D) The recitation of "the drug" in claims 29 and 30 lacks antecedent basis in claim 1.

(E) Claims 29 and 30 recite "downward slope of greater than 5% in said standard" and "a change of less than 5% of the slope of said standard". It is noted that "downward slope" and

change of less than 5% of the slope" are relative terms tied to the "standard curve. The metes and bounds of the standard curve cannot be determined because the method lacks positive active method steps for the generation of the standard curve. Slope is a function of the relative position of the two parameters which are being used to set forth a mathematical relationship. Without specifying the relative positions of the two parameters in two dimensions, the claim is indefinite as a reversal of the parameters which are represented in the X axis and the Y axis will result in a different mathematical relationship, and hence a different "slope". In the instant case, not only is the relative position of the two parameters unknown, the parameters themselves are lacking metes and bounds because section c of the claim fails to set forth any active positive steps for the construction of the "standard curve". Further, without a specific definition of what constitutes the "standard curve" the metes and bounds of section c cannot be determined.

(F) Claim 31 recites "minimal" and "maximal" dose. The terms "minimal" and "maximal" in claim 31 is a relative term which renders the claim indefinite. The term "minimal" and "maximal" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

10. Claims 1-3, 9-11, 16-18, 23, 24 and 28-32 are rejected under 35 U.S.C. 103(a) as being obvious over Tang et al (U.S. 5,880,141) in view of Foulkes et al (U.S. 5,580,722).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this

rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claim 1 is drawn to a method of determining an efficacious dose of a compound administered to a subject for the purpose of modulating angiogenesis comprising the steps of (a) administering the compound to a patient wherein the compound is a receptor antagonist that inhibits a receptor involved in angiogenesis, (b) monitoring a marker selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL8 and t-PA, (c) constructing a standard curve and (d) determining the efficacious dose based on the standard curve. claim 1 is examined to the extent that is reads on compound A. claim 2 embodies the method of claim 1 wherein conditions associated with angiogenesis include cell proliferation. Claim 3 embodies the method of claim 3 wherein the conditions associated with cell proliferation are cancer, arthritis, and endometriosis and ocular neovasularization. Claim 9 embodies the method of claim 1 wherein the marker is present in a sample obtained from said subject. Claim 10 is examined to the extent that is reads on whole blood and fractions thereof. Claim 11 embodies the method of claim 10 wherein the sample comprises monocytes. Claim 16 is examined to the extent that it reads on the detection of a protein marker. claim 17 embodies the method of claim 1 wherein the step of monitoring a marker comprises the step of determining the presence or amount of said marker. Claim 18 embodies the method of claim 17 wherein the presence or amount of said marker is detecting by an antibody. Claim 23 embodies the method of claims 16-18 wherein said marker is present in a sample collected from a subject. Claim 23 is examined to the extent that it reads on whole blood or fractions thereof which are collect3ed from a subject. Claim 24 embodies the method of claim 1 wherein the step of monitoring a marker related to angiogenesis comprises the step of comparing said marker to a standard. Claim 28 is drawn to the method of claim 1 and is examined to the extent that it reads on detecting the marker with antibodies, enzyme-linked immunosorbent assay, solid phase enzyme immunoassay with polyclonal antisera. Claim 29 embodies the method of claim 1 wherein said efficacious dose is where additional amounts of drug cause a downward slope of greater than 5% in said standard. Claim 30 is drawn to the method of claim 1 wherein additional amounts of the drug causes a change of less than 5% in

the slope of said standard. Claim 31 embodies the method of claim 1 wherein said efficacious dose is between minimal and maximal dose. claim 32 embodies the method of claim 1 wherein said marker is tissue factor.

Tang et al teach a method for screening for compounds having protein tyrosine kinase inhibitory activity by means of in vivo experiments (column 7, lines 47-54). Tang et al teach that compound A is a compound which is capable of regulating and or inhibiting tyrosine kinase signal transduction (column 3, lines 35-67). Note that column 3, line 58 indicates that X is "O", and R1 is a 5 membered heteroaryl, substitutes with C-alkly, and that R2-R5 is hydrogen. Tang et al teach that the disclosed tyrosine kinase inhibitors are intended for use in methods for treating diseases comprising proliferation or metabolic disorders, for example cancer, fibrosis, psoriasis, atherosclerosis, arthritis, and other disorders related to abnormal vasculogenesis and/or angiogenesis, such as diabetic retinopathy (column 4, lines 32-37) and that tyrosine kinase signal transduction controls cell proliferation and differentiation and that abnormal cell proliferation may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, leukemia, glioblastoma, hemangioma, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy (or other disorders related to uncontrolled angiogenesis and/or vasculogenesis) (column 6,lines 22-29). Tang et al teach that the determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided (column 12, lines 50-53) and that the therapeutically effective dose can be estimated initially from cell culture assays followed by a preclinical assay wherein a dose can be formulated in an animal model to achieve a circulating concentration range that includes the IC. 50 as determined in cell culture (i.e., the concentration of the test compound which achieves a half-maximal inhibition of the PTK activity) and that such information can be used to more accurately determine useful doses in humans. Tang et al teach that a therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms or a prolongation of survival in a patient and that toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD..50 (the dose lethal to 50% of the population) and the ED..50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between

LD 50 and ED. 50. Compounds which exhibit high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED 50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition (column 12, line 63-column 13, line 16). Tang et al also teach that dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the kinase modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data; e.g. the concentration necessary to achieve 50-90% inhibition of the kinase using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration and that bioassays can be used to determine plasma concentrations (column 13, lines 17-27). Tang et al do not specifically recite the limitation of determining a standard curve and determining the efficacious dose based on said standard curve, although the limitations appear to be inherent within the method disclosed by Tang et al. Tang et al teach the monitoring of receptor tyrosine kinase activity in cell lines by means of antibody-based detection systems (beginning in column 14, within section 6, entitled "RTK assays"). Tang et al do not teach the method wherein whole blood or fractions thereof are monitored by detecting the presence or amount of t-PA, u-PA or tissue factor.

It is noted that Tang et al teach that uncontrolled cellular proliferation can lead to atherosclerosis and vasculogenesis. Foulkes et al teach a method for modulating genes that encode a protein of interest associated with the treatment of atherosclerosis or restinosis (abstract). Foulkes et al teach that monocyte attach to the endothelium and enter into the arterial wall (column 2, lines 3-6). Foulkes et al teach that atherosclerotic plaques develop into thrombogenic plaques (column 6, lines 21-34) and that t-PA, u-PA and tissue factor as proteins which are associated with thrombosis (column 21, lines 55-67). Foulkes et la specifically teach that the plasminogen activators such as t-PA are anti-thrombogenic and plasminogen activator inhibitor is associated with thrombosis (column 6, lines 15-20).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to determine an efficacious dose for the purpose of modulating angiogenesis, comprising administering to a subject compound A, monitoring a marker in the blood or a fraction thereof taken from said patient , wherein the marker is selected from the group consisting of tissue factor, u-PA and t-PA. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Foulkes et al on u-PA, t-PA and tissue factor as proteins of interest with respect to the condition of thrombosis, and the correlation between thrombosis and atherosclerosis restinosis; and the teachings of Tang et al on methods of determining an efficacious dose of protein kinase inhibitor, and the association between cell proliferation, angiogenesis, and atherosclerosis.

11. Claims 1-3, 9-11, 16-18, 23, 24 and 28-32 are rejected under 35 U.S.C. 103(a) as being obvious over Tang et al (U.S. 5,880,141) in view of the abstract of Pierce et al (Glycoconjugate Journal, 1997, vol. 14, pp. 623-630) and Galang et al (Journal of Biological Chemistry, 1996 Vol. 271, pp. 7992-7998) .

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claim 1 is drawn to a method of determining an efficacious dose of a compound administered to a subject for the purpose of modulating angiogenesis comprising the steps of (a) administering the compound to a patient wherein the compound is a receptor antagonist that inhibits a receptor involved in angiogenesis, (b) monitoring a marker selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL8 and t-PA, (c) constructing a standard curve and (d) determining the efficacious dose based on the standard curve. claim 1 is examined to the extent that is reads on compound A. claim 2 embodies the method of claim 1 wherein conditions associated with angiogenesis include cell proliferation. Claim 3 embodies the method of claim 3 wherein the conditions associated with cell proliferation are cancer, arthritis, and endometriosis and ocular neovasularization. Claim 9 embodies the method of claim 1 wherein the marker is present in a sample obtained from said subject. Claim 10 is examined to the extent that is reads on whole blood and fractions thereof. Claim 11 embodies the method of claim 10 wherein the sample comprises monocytes. Claim 16 is examined to the extent that it reads on the detection of a protein marker. claim 17 embodies the method of claim 1 wherein the step of monitoring a marker comprises the step of determining the presence or amount of said marker. Claim 18 embodies the method of claim 17 wherein the presence or amount of said marker is detecting by an antibody. Claim 23 embodies the method of claims 16-18 wherein said marker is present in a sample collected from a subject. Claim 23 is examined to the extent that it reads on whole blood or fractions thereof which are collect3ed from a subject. Claim 24 embodies the method of claim 1 wherein the step of monitoring a marker related to angiogenesis comprises the step of comparing said marker to a standard. Claim 28 is drawn to the method of claim 1 and is examined to the extent that it reads on detecting the marker with antibodies, enzyme-linked immunosorbent assay, solid phase enzyme immunoassay with polyclonal antisera. Claim 29 embodies the method of claim 1 wherein said efficacious dose is where additional amounts of drug cause a downward slope of greater than 5% in said standard. Claim 30 is drawn to the method of claim 1 wherein additional amounts of the drug causes a change of less than 5% in the slope of said standard. Claim 31 embodies the method of claim 1 wherein said efficacious dose is between minimal and maximal dose. claim 32 embodies the method of claim 1 wherein said marker is tissue factor.

Tang et al teach a method for screening for compounds having protein tyrosine kinase inhibitory activity by means of in vivo experiments (column 7, lines 47-54). Tang et al teach that compound A is a compound which is capable of regulating and or inhibiting tyrosine kinase signal transduction (column 3, lines 35-67). Note that column 3, line 58 indicates that X is "O", and R1 is a 5 membered heteroaryl, substitutes with C-alkly, and that R2-R5 is hydrogen. Tang et al teach that the disclosed tyrosine kinase inhibitors are intended for use in methods for treating diseases comprising proliferation or metabolic disorders, for example cancer, fibrosis, psoriasis, atherosclerosis, arthritis, and other disorders related to abnormal vasculogenesis and/or angiogenesis, such as diabetic retinopathy (column 4, lines 32-37) and that tyrosine kinase signal transduction controls cell proliferation and differentiation and that abnormal cell proliferation may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, leukemia, glioblastoma, hemangioma, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy (or other disorders related to uncontrolled angiogenesis and/or vasculogenesis) (column 6,lines 22-29). Tang et al teach that the determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided (column 12, lines 50-53) and that the therapeutically effective dose can be estimated initially from cell culture assays followed by a preclinical assay wherein a dose can be formulated in an animal model to achieve a circulating concentration range that includes the IC. 50 as determined in cell culture (i.e., the concentration of the test compound which achieves a half-maximal inhibition of the PTK activity) and that such information can be used to more accurately determine useful doses in humans. Tang et al teach that a therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms or a prolongation of survival in a patient and that toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD..50 (the dose lethal to 50% of the population) and the ED..50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD 50 and ED. 50. Compounds which exhibit high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of

circulating concentrations that include the ED 50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition (column 12, line 63-column 13, line 16). Tang et al also teach that dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the kinase modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data; e.g. the concentration necessary to achieve 50-90% inhibition of the kinase using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration and that bioassays can be used to determine plasma concentrations (column 13, lines 17-27). Tang et al do not specifically recite the limitation of determining a standard curve and determining the efficacious dose based on said standard curve, although the limitations appear to be inherent within the method disclosed by Tang et al. Tang et al teach the monitoring of receptor tyrosine kinase activity in cell lines by means of antibody-based detection systems (beginning in column 14, within section 6, entitled "RTK assays"). Tang et al do not teach the method wherein whole blood or fractions thereof are monitored by detecting the presence or amount of ETS-1.

The abstract of Pierce et al teaches that the ETS family of transcriptional activators are upregulated through growth factor receptors that activate tyrosine kinases.

Galang et al teach that ETS is the downstream target of the Neu oncogene and that intervention in the upregulation of ETS may be a useful in therapy for Neu associated cancers (abstract)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to determine an efficacious dose for the purpose of modulating angiogenesis, comprising administering to a subject compound A, monitoring a marker in the blood or a fraction thereof taken from said patient , wherein the marker is ETS-1. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the abstract of Pierce et al on the activation of ETS by tyrosine kinases and the teachings of Galang et al on the association between ETS activation and cellular transformation and the suggestion of Galang et al that therapeutic intervention in Neu associated

cancers be targeted to the downstream targets of Neu which include the ETS transcription factors.

12. All other rejections and objections as set forth in Paper No. 14 are withdrawn.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
10/18/03